Important Advances in Clinical Medicine

Epitomes of Progress — Allergy

The Scientific Board of the California Medical Association presents the following inventory of items of progress in allergy. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in allergy which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy of the California Medical Association and the summaries were prepared under its direction.

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Diseases Associated With High Levels of Immunoglobulin E

ALTHOUGH NOT measuring specific antibodies, the finding of an elevated serum level of total immunoglobulin E (IgE) of greater than 50 IU per ml may have diagnostic and therapeutic implications. For example, IgE levels greater than 400 IU per ml are found in more than 75 percent of patients with atopic dermatitis. The levels tend to be even higher with more severe disease or with coexistent asthma. Modestly elevated IgE levels have also been reported in conjunction with other dermatologic conditions such as neurodermatitis, contact dermatitis, dyshidrotic dermatitis, psoriasis, urticaria, alopecia areata and burns.

Although modestly elevated IgE levels are often found in patients with extrinsic asthma and are sometimes observed in patients with allergic rhinitis without asthma or eczema, levels found in these patients overlap those found in patients with nonatopic nasal and chest symptoms. Consequently, the total serum IgE level by itself does not reliably differentiate between allergic and nonallergic respiratory symptoms. Total serum IgE levels of less than 50 IU per ml do not exclude demonstrable specific IgE in specific patients with rhinitis, asthma or eczema.

Serum IgE levels greater than 500 IU per ml are characteristically found in patients with active helminthic infections involving organisms with a prominent tissue phase, such as schistosomiasis, filariasis, echinococcosis, strongyloidiasis, ascariasis, hookworm disease and trichinosis. IgE levels greater than 1,000 IU per ml are almost always found in patients with allergic bronchopulmonary aspergillosis, where the level of total serum IgE correlates with the activity of the disease. The IgE level may rise before a clinically defined exacerbation and subsequently fall with appropriate treatment.

Elevated serum IgE levels have also been reported in certain patients with Churg-Strauss syndrome, Wegener's granulomatosis, chronic eosinophilic pneumonia, Hodgkin's disease, sporadic bronchiolitis, childhood renal disease with proteinuria, and the hypereosinophilic syndrome. The significance of the elevated IgE levels in the development of these illnesses is largely unknown. However, in the hypereosinophilic syndrome, patients with elevated IgE levels tend to possess

fewer leukemic markers, are more responsive to corticosteroid therapy and have a better prognosis.

A syndrome has been recently defined which includes these characteristics: eczema, susceptibility to recurrent cutaneous and respiratory staphylococcal infections, a neutrophil chemotactic defect in autologous serum, variable T cell dysfunction, and substantially elevated levels of IgE (usually greater than 5,000 IU per ml). Elevated IgE levels have also been found occasionally in patients with other immunodeficiency disorders such as DiGeorge's syndrome, Nezelof's syndrome and chronic granulomatous disease The highest levels of circulating IgE are found, however, in those rare patients with IgE myeloma.

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Allergic Interstitial Nephritis

MORE THAN 300 cases of drug-induced allergic interstitial nephritis have been reported, constituting 3 percent to 8 percent of all cases of acute renal failure. The drug most often responsible for this disease is methicillin, although several other drugs have produced a similar allergic reaction.

The onset of symptoms is usually sudden, with evidence of renal impairment or frank renal failure occurring five days to five weeks after first administration of the drug. Oliguria with protein and cells in the urinary sediment is accompanied by rash, fever and arthralgias. Eosinophilia in blood and urine and increased levels of serum immunoglobulin E (IgE) are typical but are not found in all cases. The diagnosis is most often missed when the reaction complicates preexisting renal disease.

If the disease has been caused by administration of a drug, there is usually prompt remission of symptoms and signs when administration is discontinued. Often, however, the diagnosis is not suspected until after a renal biopsy has been done, which shows tubular interstitial edema and a patchy infiltrate of lymphocytes, plasma cells and eosinophils in the absence of significant glomerular or vascular disease. Recently, Linton and associates have shown that gallium citrate scintigraphy of the kidneys produces a substantial uptake of the isotope, which resolves in six weeks after the offending drug is withdrawn. The only other disease showing similar intense uptake is minimal change nephrotic syndrome, but usually this can be differentiated from allergic interstitial nephritis on clinical grounds. If this diagnostic technique is confirmed by further studies, it will lessen the need to do diagnostic renal biopsies.

The allergic nature of the disease is strongly suggested by the onset of fever, rash, joint symptoms and eosinophilia within days after the drug is given. Evidence suggests that several mechanisms may be operative. The eosinophilia and elevated IgE levels found in most cases suggest IgE-mediated disease, although wheal and erythema skin tests with the drugs in question are usually negative. The mononuclear cell infiltrate in the tubules is consistent with a cell-mediated process. The presence of immune complexes in renal tubules demonstrated by light or electron microscopy has been shown in only a few of the cases in which such complexes have been sought. In one patient, circulating antitubular basement membrane antibody was detected, suggesting that the drug might have triggered an autoimmune process in that case. No studies have been successful in producing the disease in animals so that information about immunopathogenesis must be inferred from further clinical studies.

Diagnosis requires a strong index of suspicion in any patient in whom renal insufficiency of sudden onset develops that cannot be explained on the basis of hypotension or sepsis. Although a renal biopsy can provide a definitive diagnosis, it is not necessary if clinical improvement occurs promptly after removal of the allergenic drug. Allergic interstitial nephritis should not be confused with analgesic nephropathy, a toxic reaction resulting in chronic tubular interstitial nephritis with tubular damage and fibrosis. This latter disease is associated with ingestion of high doses of analgesic drugs, most often phenacetin, and is found especially in drug abusers.

If allergic interstitial nephritis is diagnosed early, discontinuance of the drug will usually result in rapid recovery. Delay in diagnosis may necessitate hemodialysis because of severe renal damage. Reports of beneficial effects from corticosteroid therapy are difficult to evaluate because of inadequate controls, although such treatment is probably indicated if recovery is slow but uncom-